PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/002936	13.08.2004	14.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/00, C07K14/00, A61K47/48, C12N5/20, C07K19/00, A61K45/00, A61K47/00, C07K16/46, C12N1/15,

Applicant
DIATOS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/002936

10/568108

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/002936

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

   see separate sheet

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

   see separate sheet

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 01/64738 A (AVRAMEAS EUSTRATE ; DIATOS S A (FR); TERNYNCK THERESE (FR)) 7 September 2001 (2001-09-07)
D2: WO 03/018636 A (AVRAMEAS E. ; DIATOS S A (FR)) 6 March 2003
D3: WO 03/106491 A (MEIKAS ANNE ; SOOMETS URSEL (EE); KOGERMAN PRIIT (EE); POOGA MARGUS (E) 24 December 2003 (2003-12-24)
D4: WO 03/092736 A (FRANDSEN TORBEN PETER ; PANTHECO AS (DK); TOLBORG JAKOB (DK); JOHANSEN) 13 November 2003 (2003-11-13)
D5: WO 94/28921 A (DEMETER BIOTECH LTD) 22 December 1994
D6: WO 99/07414 A (SARON MARIE FRANCOISE ; BLONDEL BRUNO (FR); BUTTIN GERARD (FR); ZIPETO) 18 February 1999 (1999-02-18)
D7: NIIDOME TAKURO ET AL: "Chain length of cationic alpha-helical peptide sufficient for gene delivery into cells" BIOCONJUGATE CHEMISTRY, vol. 10, no. 5, September 1999 (1999-09), pages 773-780,
D8: AVRAMEAS A ET AL: "Efficient gene delivery by a peptide derived from a monoclonal anti-DNA antibody" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 10, no. 1, January 1999, pages 87-93,

1. Objections under Article 33(2) PCT (Novelty)

1.1 The opinion has been established under the assumption of valid priority rights. Should this however not be the case, the documents D3 and D4 cited in the ISR as P-document might become important. Moroever, the earlier D3 and D4's content as filed might be considered as comprised in the state of the art relevant to the question of novelty in the regional phase.

1.2 The consensus sequence in claim 1 is very broad and it is not clear if all the amino acid sequence falling within the scope of the claim 1 is able to facilitate penetration of a substance of interest (see Art. 5 and 6 PCT remarks). However, although many documents are dealing with peptides allowing cell penetration with an attached "cargo" (e.g. see D1-D2), no prior art unambiguously disclosed the exact sequences as claimed in dependant claims 3-18 and consensus sequence in claim 1. Therefore, novelty of the subject-matter of claims 1-28 can be acknowledged.

2. Objections under Article 33(3) PCT (Inventive step)

The application relates to amino acid sequences facilitating the penetration of a sequence of interest into cells and/or cell nuclei.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative cell penetrating peptide sequence.

The solution to this technical problem are the sequences of claim 1-18 of the present application.
These sequences distinguish themselves from the known sequences in D1-D2 by their primary structure.
However, merely describing a novel peptide sequence is not sufficient to establish inventive step. In the absence of any unexpected technical effect, such an sequence can considered to be the result of an arbitrary selection from a larger number of possible solutions to the above mentioned problem.

As acknowledged in the description (page 1-6), several prior art already deal with a similar subject-matter. As also seen from D5-D8, different peptides exist which are able to deliver gene into cells.

One of the main features of different cell-penetrating peptides, such as the one disclosed in D1-D2, is the high content of basic residues contained in various "consensus" sequence. The general consensus sequence claimed in the present application only differs in a few X-residue "spacers" (e.g. XB(B)BXBXXB instead of XBBBXXBX or XBBXBX in D1). If compared to other peptide murine sequences disclosed in D6 (as claimed on page 6 of the description) present sequences have additional properties, this surprising technical features should be clearly assigned to a "structural" motif for which these properties have been clearly demonstrated. Otherwise, the subject-matter of claims 1-28 would not appear to involve any technical teaching which can be considered as inventive in view of D1-D2's disclosure in line with D6 and the routine knowledge of a person skilled in the art (e.g. the skilled artisan would find obvious to screen variation of known peptides motifs for providing alternative peptide sequences allowing cell penetration).

Consequently, at present, no inventive step can be acknowledged for the claims

1-28. Thus these claims do not meet the requirements of Article 33(3) PCT.

3. Sufficiency of disclosure (Art. 5 PCT)

The applicant should keep in mind that the guiding principle is always that the skilled person should, after reading the description, be able to readily perform the invention over the whole area claimed without any undue burden and without inventive skill. Present claims 1-18 relate to an extremely large number of possible amino-acid sequences. Support within the meaning of Article 5 PCT is to be found, however, for only a portion of the polypeptides claimed. In the present claims, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible.
As mentioned in the ISR, the search has been carried out for those part of the claims which appear to be supported, and disclosed in the examples.
Examples 1-4 show a limited number examples of peptide sequences and their combination with "substance of interest", regarding the thousands of possibilities encompassed by the broad wording of the claims (e.g. claim 1). Moreover, no experimental comparison with known peptides sequence is given in order to show a surprising technical features linked to a specific structural motif.

4. Clarity

The wording "substance of interest" used throughout the claims lacks clarity under Article 6 PCT.